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(54) PROCESS AND APPARATUS FOR BLOOD FRACTIONATION

(71) We, AMICON CORPORATION, a corporation organized under the Laws of the State of Massachusetts, United States of America, of 25 Hartwell Avenue, Lexington, Massachusetts, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention is concerned with a process and apparatus for fractionating blood.

When obtaining blood from a blood donor, it is very often desirable to be able to return the cellular components to the donor so that more frequent bleedings can be made. When only the plasma component of the blood is desired for emergency use, the formed elements of the blood (which include the red blood cells, white blood cells and platelets) can be discarded or used for other purposes or can profitably be returned to the donor. Such a return is particularly important because (1) it allows the donor to recuperate to a state where he can donate again within two weeks rather than in about 2 months as is the case when the non-plasma component of the blood is not returned to him, and (2) it avoids the temporary weakness suffered by some donors after they donate a pint of blood. The importance of a donor's being able to contribute blood at relatively frequent intervals is obvious in circumstances such as those wherein injuries are incurred during military operations or wherein a donor bears a rare blood-type for which an emergency need exists.

However, blood fractionating of the type described is not used as frequently as desirable because no really convenient means for carrying out the process has been available

into a blood bag by means known to most blood donors, then

(2) transferring the blood bag into a centrifugal separating apparatus, then

(3) "spinning" the blood at a rate which optimizes the separation of plasma from other blood components, but substantially avoids damage to blood cells, then

(4) separation of plasma by bag compression or withdrawal to a receiving vessel, and finally

(5) returning the formed elements back into the patient by the usual transfusion techniques.

Not only does this process involve relatively expensive apparatus, but it also comprises a sufficiently large number of handling steps to significantly increase the chance of contamination and/or cellular damage in the relatively crude environments of the type that may be encountered at accident scenes, in military operations, etc.

Moreover, there are many situations in which it is desirable to separate blood components without returning any of them to the donor in order to use diagnostic tests without interference from either the formed cell or plasma components thereof.

We have now developed a process and apparatus for effecting the simple fractionation of whole blood into a plasma component and a cellular component while subjecting the components to only very slight stress. The process is readily applicable to blood-donation procedures, making it possible to return the non-plasma component or fraction to the donor virtually simultaneously with the donation.

According to the present invention, we provide a process for separating blood plasma from the other components of blood, which

comprises

having a depth of up to 20 mils measured vertically from the face of the membrane, while applying sufficient pressure to the whole blood to maintain a pressure differential between the opposite faces of the membrane of from 1 to 15 p.s.i. and a flow velocity of the whole blood across the face of the membrane of from 2 to 50 feet per minute, and collecting from the other face of the membrane the plasma component of the blood and from the end of said flow path the non-plasma components of the blood.

The present invention also comprises apparatus for carrying out the separation of whole blood into a plasma fraction and a cellular fraction, which comprises a reservoir for holding whole blood which is to be fractionated, a porous filter membrane having effective pore diameters of from 0.1 to 0.8 micron, means for directing a flow of whole blood from the reservoir across one face of the filter membrane in a flow path having a depth of up to 20 mils measured vertically from the face of the membrane, and pressure applying means for applying a pressure to the whole blood so as to be capable of maintaining the flow of whole blood at a pressure differential between the opposite faces of the membrane of from 1 to 15 p.s.i. and at a flow velocity across the face of the membrane of from 2 to 50 feet per minute.

The precise diameter of the pores within the stated range of size which gives best results depends upon the precise pressure differential employed, higher pressure differentials within the stated range requiring smaller pore diameters. The pressure differential is critical because it provides the driving force for controlling the velocity of the blood across, and plasma through the membrane, and also affects the degree of hemolysis which occurs during filtration. In general, it is preferred that the pore diameters should be from 0.4 to 0.7 micron.

It is essential that the blood being fractionated should travel in a path substantially parallel to and at a depth of up to 20 mils from the membrane surface. Attempts to utilize the same membranes under conditions in which the whole blood is forced through the membrane by conventional filtration technique (i.e., putting the blood in a reservoir over a filter membrane and applying a pressure difference across the membrane to push or pull the plasma fraction through the membrane) results in almost immediate "plugging" of the membrane.

The term "filter membrane" is used in this specification to mean that class of filters normally supplied in thin sheet form and

brane is preferred when conveniently available, but a particularly surprising feature of the invention is that homogeneous depth filters may be utilized in the blood separation process.

The filtration process of the invention is carried out at relatively low pressure differentials, that is, from 1 to 15 p.s.i., as measured from one side of the filter membrane to the other. As a matter of convenience, both the receptacle for the filtrate (plasma) and for the rejected blood (non-plasma fraction) are preferably maintained at atmospheric pressure. Pressure differentials near the lower end of this range, that is from 1.5 to 5 p.s.i. are most advantageous, in part because they can be utilized in equipment which is less rigorously designed to avoid undue stress on the cells contained in the blood being fractionated. Likewise, the velocity across the face of the membrane is relatively low, that is in the range of from 2 to 50 feet per minute. Under these conditions the flow is substantially laminar. The blood, after passing over the surface of the membrane, is preferably recycled back to the whole blood reservoir; the velocity of the recycle stream as it is introduced into the contents of the reservoir aids in keeping the blood mixed well.

In order that the invention may be more fully understood, preferred embodiments of the process and apparatus will now be described, by way of example only, with reference to the accompanying drawings, in which:

Figure 1 is an elevation, partly in section of a first embodiment of apparatus;

Figure 2 is a perspective view from the bottom of the reservoir and flow-directing means of the apparatus of Figure 1;

Figure 3 is an exploded view in perspective of another embodiment of apparatus comprising means for attaching a hypodermic needle thereto; and

Figure 4 is an elevation showing the apparatus of Figure 3 in operation.

Referring to Figures 1 and 2, it is seen that an ultra-filtration cell 10 comprises a top cap 12, a bottom cap 14 and a cylinder assembly 16. The cylinder is compressed and sealed between caps 12 and 14 by means of toggle clamping assembly 18, top O-ring seal 20, and bottom O-ring seal 22.

Top cap 12 comprises a pressure relief valve 24 and a means to drive fluid across the membrane comprising a port 25 adapted for connection to a pressurized gas source for pressurizing liquid in reservoir 28.

Resting on bottom cap 14 is a macroporous support plate 30 formed of sintered poly-

is compressed against the outer periphery of membrane 32, thereby providing an efficient edge sealing means.

Cylinder assembly 16 comprises reservoir 28 and an aperture 34 leading from reservoir 28 into a spiral flow path 36 which is formed by spiral grooves 38 on the bottom surface 39 of assembly 16. This flow path 36 is 0.125 inch wide and 0.010 inch (10 mils) high. It follows a spiral path parallel to the membrane surface, terminating at a fluid outlet port 40 through which the retained liquid may, via conduit 41, be collected or recycled for another concentrating step. Filtrate, i.e., that fraction of material which comes through the filter is carried out of the cell through conduit 42 which is machined into bottom cap 14.

A sample of whole blood (treated with ACD) was inserted into reservoir 28 and, under a 2 p.s.i.g. driving force, was divided into a plasma fraction and a cellular fraction. The whole blood was forced through aperture 34 in cylinder assembly 16, and thereupon is caused to follow spiral flow path 36 over the surface of membrane 32. The blood plasma fraction passed through the filtration membrane, and was collected through conduit 42 at atmospheric pressure. About 60% of the plasma content of the blood was recovered and there was no evidence of hemolysis in the plasma so collected.

Although the optimum operation of the illustrated device was realized with an operating pressure of from 2 to 4 p.s.i.g., it is stressed that higher operating pressures may be used when particular care is taken to smooth blood-contacting surfaces in such a way as to avoid excessive mechanical shear on the formed elements of the blood. For example, a streamlined or smooth-surfaced wall 49 with gently rounded corners of aperture 34 is advantageous in this respect. In general, however, a low-pressure process is most desirable for use in emergency blood-donation procedures.

Another embodiment of the apparatus is shown in Figure 3. In this apparatus, which is most useful in analytical work, a hypodermic syringe 50 has been utilized to withdraw a blood sample from a patient. The needle (not shown) of the syringe is then removed and the syringe is attached, by means of a fastening means 52, such as Luer lock 54, to filtration cell 56. Filtration cell 56 comprises a top retaining plate 58, filtration membrane 60, a sintered porous polyethylene support disc 62, and a bottom retaining plate 64.

Retaining plate 58 comprises a spiral ridge forming a shallow flow path 66 having a depth of 6 mils, a width of 0.5 cm., and a

filtration results, it is desirable to provide the above-described apparatus with a positive pressure generating means rather than to rely upon the manual pressure exerted by a number of different operators on the pressure applying means (the piston of the syringe). To provide this pressure generating means, therefore, a spring means 72 is mounted, at one end 74 thereof, on projecting outlet port 71. The other end 76 of the spring is adapted to press on plunger 78 of the hypodermic syringe 50. When spring means 72 is so mounted as to rest on plunger 78, a controlled amount of pressure, about 2.5 p.s.i., is generated for filtering the blood. Another advantage is that one operator can utilize a number of these devices at a single time since they do not require close attention during the filtration operation.

Figure 4 shows a schematic diagram showing the analytical device of Figure 3 in operation. A plasma fraction of the blood is being collected in vessel 82 while the other blood components are being collected in vessel 80.

Using the cellulosic ester membrane described above, less than 0.1% hemolysis was observed, and the plasma obtained was not detectably different from that obtained by conventional centrifugation. From a 10 ml. sample of fresh blood of normal hematocrit, there was obtained, in a filtering time of 15 to 20 minutes, approximately 3.0 to 3.4 ml. of plasma.

WHAT WE CLAIM IS:—

1. A process for separating blood plasma from the other components of blood, which comprises conducting the whole blood in a flow path parallel to one face of a porous filter membrane having effective pore diameters of from 0.1 to 0.8 micron, the path having a depth of up to 20 mils measured vertically from the face of the membrane, while applying sufficient pressure to the whole blood to maintain a pressure differential between the opposite faces of the membrane of from 1 to 15 p.s.i. and a flow velocity of the whole blood across the face of the membrane of from 2 to 50 feet per minute, and collecting from the other face of the membrane the plasma component of the blood and from the end of said flow path the non-plasma components of the blood.

2. A process according to claim 1, in which the filter membrane has pore diameters of from 0.4 to 0.7 microns.

3. A process according to claim 1 or 2, in which the pressure differential is from 1.5 to 5 p.s.i.

4. Apparatus for carrying out the separation of whole blood into a plasma fra-

to 0.8 micron, means for directing a flow of whole blood from the reservoir across one face of the filter membrane in a flow path having a depth of up to 20 mils measured vertically from the face of the membrane, and pressure applying means for applying a pressure to the whole blood so as to be capable of maintaining the flow of whole blood at a pressure differential between the opposite faces of the membrane of from 1 to 15 p.s.i. and at a flow velocity across the face of the membrane of from 2 to 50 feet per minute.

5. Apparatus according to claim 4, in which the reservoir is the barrel of a hypodermic syringe, the pressure applying means comprises the piston of the syringe, and the syringe is detachably connected to the flow directing means.

6. Apparatus according to claim 5, which additionally comprises a spring for moving the piston in the barrel of the syringe so as to generate said pressure differential and flow velocity.

7. Apparatus according to any of claims 4 to 6, in which the filter membrane has pore diameters of from 0.4 to 0.7 micron.

8. A process for separating blood plasma from the other components of blood according to claim 1 substantially as herein described with reference to Figures 1 and 2 or Figures 3 and 4 of the accompanying drawings.

9. Apparatus for carrying out the separation of whole blood into a plasma fraction and a cellular fraction according to claim 4 substantially as herein described with reference to Figures 1 and 2 or Figures 3 and 4 of the accompanying drawings.

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1283273 COMPLETE SPECIFICATION

2 SHEETS *This drawing is a reproduction of the Original on a reduced scale*

Sheet 1

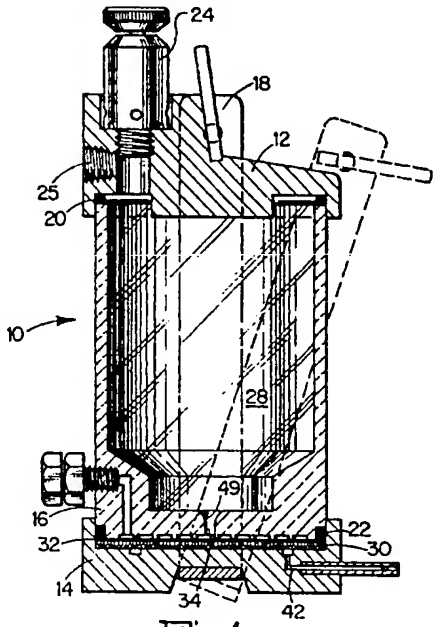

Fig. 1.

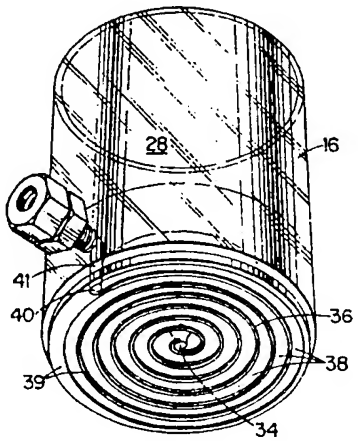

Fig. 2.

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Sheet 2

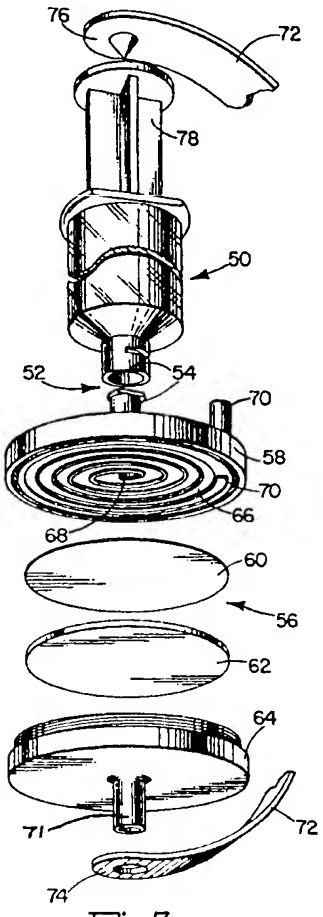

Fig. 3.

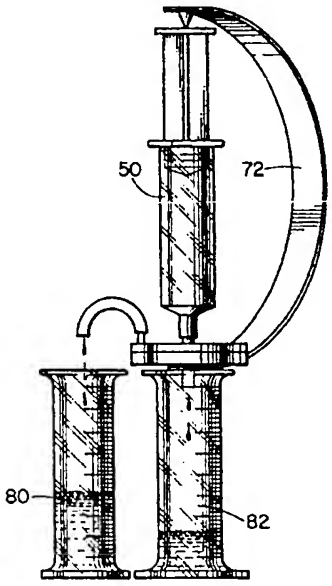

Fig. 4.